IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No.:	SJ-0015
Inventors:	Sorrentino and Schuetz
Serial No.:	09/866,866
Filing Date:	May 29, 2001
Examiner:	Li, Qian J.
Group Art Unit:	1632
Title:	Method of Identifying and/or Isolating Stem Cells and Prognosing Responsiveness to Leukemia Treatment

DECLARATION

1. I, Dr. Balazs Sarkadi, M.D., Ph.D. am a medical doctor affiliated with National Medical Center in Budapest, Hungary. Based upon my qualifications as set forth in the attached curriculum vitae and list of publications, I am an expert in the field of ABC transporters, especially as it pertains to the generation of antibodies to ABC transport proteins including BCRP.

2. I have reviewed the Office action issued in this case dated May 21, 2003. I have further reviewed and understand the prior art methods taught by Ross (U.S. Patent 6,313,277) and

Niman (U.S. Patent 5,563,247) as identified by the Examiner in the Office action.

3. As of the priority date of May 31, 2000 there was no method known in the art to reliably produce an isolated antibody that recognizes an extracellular portion of the ABC transporter BCRP(ABCG2) in a living cell. One of skill in this field would not have expected that conventional methods available for generating antibodies as of May 31, 2000 could be used to generate an antibody that would specifically recognize the extracellular portion of BCRP on a cell.

4. In particular, someone skilled in the field of antibody production would not have reasonably expected to be able to produce an antibody that recognizes the extracellular portion of BCRP in its natural conformation, using the prior art methods taught by Ross (U.S. Patent 6,313,277) and Niman (U.S. Patent 5,563,247), as suggested by the Examiner.

5. Ross teaches antibodies prepared against a purified protein. A purified protein can have a very different conformation than the conformation that exists when the protein is in its natural state (i.e. natural conformation). ABC transporter proteins, particularly including BCRP, adopt a very

different conformation when they are purified compared to their natural conformation imbedded in the cell membrane. With respect to the extracellular domain of BCRP, it is important to note that BCRP forms a homodimer. The BCRP homodimer would be expected to adopt a very different conformation than the monomeric purified protein or purified protein fragment. As a result, any antibody generated against a purified BCRP protein, or fragment of a BCRP protein would not be expected to recognize the extracellular domain of the BCRP protein in its natural conformation embedded in the cell membrane.

6. The Niman reference discloses a method of making an antibody to a cell surface protein by using a whole cell technique. This general technique of using whole cells as immunogens to generate antibodies to extracellular epitopes of cell membrane proteins does not work well for ABC transporters. ABC transporters, particularly those such as BCRP, are only weakly expressed and have only a few small extracellular domains which are poor targets for antibodies. Therefore, the

method for generating antibodies disclosed in Niman would not be expected to successfully generate antibodies to the extracellular domain of BCRP.

I hereby declare that all statements herein of our own knowledge are true and that all statements made on information or belief are believed to be true; and further that these statements were made with the knowledge that willful statements and the like so made are punishable by fine or by imprisonment, or both under §1001 of Title 18 of the United States Code, and that such willful statements may jeopardize the validity of the application, any patent issuing there upon, or any patent to which this verified statement is directed.

Dr. Balazs Sarkadi, M.D., Ph.D.

Date: Octobe 27/2003

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CURRICULUM VITAE

Name: Balázs Sarkadi, M.D., Ph.D., D.Sc.
Occupation: Head of Department, Scientific Deputy Director
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(phone: 36-1-395-1816)
Office: National Medical Center, Institute of Haematology and Immunology, Diószegi u. 64, 1113 Budapest, Hungary, (phone/fax: 36-1-372-4353)
Date and place of birth: May 30, 1948, Budapest, Hungary
Citizenship: Hungarian
Family status: Married, two children (born in 1974 and 1979)
Education:
- Semmelweis University Medical School, Budapest, Hungary, 1966-1972;
- M.D. degree: Budapest, 1972;
- Ph.D. degree: Hungarian Academy of Sciences, 1980;
- Doctor of Biological Sciences: Hungarian Academy of Sciences, 1986

Postdoctoral and research appointments:
- National Institute of Haematology and Blood Transfusion, Dept. Cell Metabolism, Budapest, 1972 - present;
- The University of Chicago, Dept. Physiology, Research Associate, 1976-77;
- The Hospital for Sick Children, Dept. Cell Biology, Visiting Associate Professor, 1982-1983;
- The University of North Carolina at Chapel Hill, Visiting Professor, 1990-91; Fulbright Visiting Professor, 2000-2001.
- Hungarian Academy of Sciences, Head of Membrane Biology Research Group, 1996-

Teaching activities:
- 2nd Institute of Biochemistry, Semmelweis Medical University, (courses for graduate students), 1978-81;
- Postgraduate courses in haematology and immunology, 1972 - present;
- Institute of Physiology, Semmelweis Medical University, appointment in teaching general physiology, 1985-1992;
- Full professor habilitation at Semmelweis Medical University, 1995 (biology);
- Ph. D. programs in membrane biochemistry and immunology, Semmelweis Medical University and Eotvos Lorand University, from 1994.

Memberships:
- International Society of Haematology;
American Society of Biochemistry and Molecular Biology
- New York Academy of Sciences;
- American Physiological Society (corresponding member);
- International Cell Research Organization (UNESCO - ICRO panel convenor);
- Hungarian Society of Biochemistry (vice-president);
- Hungarian Biophysical Society;
- FEBS Advanced Course Committee member, 1999-2001;

Editorial experience:
- Haematologia, managing editor, 1978-82;
- Editor of "Genetics, Structure and Function of Blood Cells", 1980;
- Editor of Biochimica Biophysica Acta, Reviews on Biomembranes,
- Reviewer for Biochimica Biophysica Acta, Cell Calcium, J. Membrane Biology, Haematologia.

Organization of Scientific Meetings:
- International Congress of Haematology, Congress Secretary (1982);
- 20th FEBS Meeting, Secretary of Scientific Program Committee (1990);
- FEBS/ICRO Advanced Courses on "Biochemistry of Membrane Transport", 1989, 1993, 1995, 1998,
- President of the Scientific Committee, FEBS-IUBMB Congress, Budapest, 2005.

Awards:
- Research Awards of the Hungarian Academy of Sciences, 1982, 1986;
- Howard Hughes International Fellowship, 1995-1999; 2000-2004;
- Bela Tanko Award (Hung. Biochem. Soc.), 1995;
- Szechenyi Research Professorship, Hungary, 1997;
- Fulbright Senior Research Fellowship, 2000;
- Research Award of the Hungarian Academy of Sciences, 2003.

Symposium or plenary lectures at International Meetings:
- Conference on "Transport ATPases", New York Acad. Sci, New York, 1982;
- Conference on "Structure and Function of Erythrocytes" Berlin, 1986;
- Symposium on the "Regulation of Cell Volume", 2nd European Congress of Cell Biology, Budapest, 1986;
- Symposium on "Membrane Transport Enzymes", FEBS Meeting, Ljubljana, 1987;
- Symposium on "Calcium Ions and Phosphoinositides", 14th Congress of the IUB, Prague, 1988;
- ICRO Symposium on "Signals and Signal Transduction in the mune System", Eger (Hungary), 1989;
- Symposium on "Calcium Transport and Calcium Signaling", th FEBS Meeting, Budapest, Hungary, 1990;
- Semmelweis International Symposium on "Calcium transport and calcium pools in human platelets", Budapest, Hungary, 1992;
- Symposium and Advanced Course on "ATP-binding Cassette Transporters", Gosau, Austria, 1997;
- 25th FEBS Meeting, Symposium on Transport ATPases, Copenhagen, Denmark, 1998;
- 26th FEBS Meeting, Symposium on ABC Transporters, Nice, France, 1999;
- Plenary lecturer, International Union of Biochemistry and Molecular Biology (IUBMB) Meeting, Birmingham, UK, 2000;
- Symposium and Advanced Course on "ATP-binding Cassette Transporters", Gosau, Austria, 2003;

Publications: see separate list
(over 110 full papers, with a total citation number of about 4,500).

Balazs Sarkadi - LIST OF PUBLICATIONS

Reviews and book chapters:

1. Gárdos, G., Szász, I. Sarkadi, B.:
Mechanism of Ca-dependent K transport in human red cells.
In: Biomembranes: Structure and Function, (eds. G. Gárdos, I. Szász), Akadémiai Kiadó, Budapest. North Holland P.Co. Amsterdam, pp. 167-180, (1975)

2. Sarkadi, B., Tosteson, D.C.:
Active cation transport in human red cells.
In: Membrane Transport in Biology, Vol. 2. (eds. G. Giebisch, D.C. Tosteson, and H.H. Ussing), Springer Verlag, Berlin, pp.117-160, (1978)

3. Sarkadi, B., Enyedi, A., Szász, I., Gárdos, G.:
Effect of calmodulin on active calcium uptake and membrane phosphorylation in inside-out red cell membrane vesicles.
In: Genetics, Structure and Function of Blood Cells (eds. S.R. Hollan, G. Gárdos, B. Sarkadi), Pergamon Press, Akadémiai Kiadó, Budapest, pp. 181-188 (1980)

4. Szász, I., Sarkadi, B., Gárdos, G.:
Calcium-sensitivity of calcium dependent functions in human red blood cells.
In: Genetics, Structure and Function of Blood Cells, (eds. S.R. Hollán, G. Gárdos, B. Sarkadi), Pergamon Press, Akadémiai Kiadó, Budapest, pp. 211-222 (1980)

5. Sarkadi, B., Szebeni, J., Gárdos, G.:
Effects of calcium on cation transport processes in inside-out red cell membrane vesicles.
In: Membrane Transport in Erythrocytes, Alfred Benson Symposium 14. (eds, U.V. Lassen, H.H. Ussing, J.O. Wieth), Munksgaard, Copenhagen, pp. 220-231, (1980)

6. Gárdos, G., Szász, I., Sarkadi, B., Szebeni, J.:
Various pathways for passive cation transport in red cells.
In: Membrane Transport in Erythrocytes, Alfred Benson Symposium 14. (eds. U.V. Lassen, H.H. Ussing, J.O. Wieth), Munksgaard, Copenhagen, pp. 163-174, (1980)

7. Sarkadi, B.:
Active calcium transport in human red cells.
Biochem. Biophys. Acta, Reviews on Biomembranes, 604, 159-190, (1980)

8. Sarkadi, B., Szász, I., Gárdos, G.:
Calcium and calmodulin in the regulation of blood cell functions.
Haematologia 14, 121-136, (1981)

9. Grinstein, S., Rothstein, A., Sarkadi, B., Gelfand, E.W.:
Responses of human lymphocytes to anisotonic media: volume-regulating behaviour.
Am. J. Physiol. 246, C204-C215, (1984)

10. Sarkadi, B., and Gárdos, G.:
Calcium-induced potassium transport in cell membranes.
In: Enzymes of Biological Membranes, 2nd ed. (A. Martonosi, ed.), Vol. 3, pp. 193-234, Plenum Publ. Co. (1985)

11. Sarkadi, B., and Gárdos, G.:
Drug actions on potassium fluxes in red cells.
In: The Red Cell Membrane: A Model For Solute Transport, (B.U. Raess and G.Tunnicliff, eds.), Humana Publ. Co, (1989)

12. Sarkadi, B., Parker, C.:
Activation of ion transport pathways by changes in cell volume.
Biochim. Biophys. Acta, Reviews on Biomembranes, 1071, 407-427, (1991)

13. Homolya, L., Müller, M., Holló, Zs., Sarkadi, B.:
Fluorescence assay for studying P-glycoprotein function at single cell level.
In: Fluorescence Microscopy and Fluorescent Probes, pp. 241-245, (J. Slavik, ed.) Plenum Press, NY, (1996)

14. Sarkadi, B., Müller, M. :
Search for specific inhibitors of the multidrug transporters.
Sem. Cancer Biol. 8, 171-182 (1997)

15. Váradi, A., Tusnády, G.E., Bakos, É., Sarkadi, B.:
Membrane topology of the human multidrug resistance-associated protein (MRP) and its homologs.
Cytotechnology 27, 71-79 (1998), and In: Multiple Drug Resistance in Cancer 2, M. Clynes, ed., Kluwer Acad. Pub, pp. 71-80 (1998)

16. Klein, I., Sarkadi, B., Váradi, A.:
An inventory of the human ABC proteins.
Biochim. Biophys. Acta. 1461, 237-262 (1999)

17. Váradi, A., Szakács, G., Bakos, É., and Sarkadi, B.:
P glycoprotein and the mechanism of multidrug resistance.
In: Mechanism of Drug Resistance in Epilepsy – Lessons from Oncology.
John Wiley and sons, LTD, Novartis Foundation, pp. 54-68 (2002).

18. Szakács, G., and Sarkadi, B.:
Multidrug resistance in cancer and modulation of drug effects by ABC transporters. In: Molecular Pathomechanisms and New Trends in Drug Research, Harwood Acad. Publ., The Netherlands, 2003.

19. Váradi, A., Tusnády, G.E., and Sarkadi, B.:
Membrane topology of ABC transporters. In: ABC Proteins: From Bacteria to Man, Elsevier, 2003.

Publications in international journals:

1. Spät, A., Sarkadi, B., Intódy, Zs., Körner, A., Szántó, J.:
Effect of renal papillary lipids and prostaglandin E-2 on corticosteroid production in the rat.
Acta Physiol. Acad. Sci. Hung. 40, 187-199, (1971)

2. Sarkadi, B., Schubert, A.:
Energy consumption of active sodium transport in isolated frog skin.
Acta Biochim. Biophys. Acad. Sci. Hung. 7, 367-376, (1972)

3. Goldschmidt, B., Sarkadi, B., Gárdos, G., Matlary, A.:
Platelet production and survival in cyanotic congenital heart disease.
Scand. J. Haematol. 13, 110-115, (1974)

4. Szász, I., Sarkadi, B., Gárdos, G.:
Erythrocyte parameters during induced Ca-dependent rapid K-efflux: optimum conditions for kinetic analysis.
Haematologia 8, 143-151, (1974)

5. Sarkadi, B., Szász, I., Gárdos, G.:
The use of ionophores for rapid loading of human red cells with radioactive cations for cation pump studies.
J. Membrane Biol. 26, 357-370, (1976)

6. Sarkadi, B., Szász, I., Gerlóczi, A., Gárdos, G.:
Transport parameters and stoichiometry of active calcium ion extrusion in intact human red cells.
Biochim. Biophys. Acta 464, 93-107, (1977)

7. Schubert, A., Sarkadi, B.:
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9. Gárdos, G., Szász, I., Sarkadi, B.:
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10. Szász, I., Sarkadi, B., Gárdos, G.:
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Brit. J. Haematol. 39, 559-568, (1978)

11. Szász, I., Sarkadi, B., Schubert, A., Gárdos, G.:
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12. Sarkadi, B., Macintyre, J.D., Gárdos, G.:
Kinetics of active calcium transport in inside-out red cell membrane vesicles.
FEBS Letters 89, 78-82, (1978)

13. Pandey, G.B., Sarkadi, B., Haas, M., Gunn, R.B., Davis, J.M., Tosteson, D.C.:
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J. Gen. Physiol. 72, 233-247, (1978)

14. Sarkadi, B., Alifimoff, J.K., Gunn, R.B., Tosteson, D.C.:
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J. Gen. Physiol. 72, 249-265, (1978)

15. Szász, I., Sarkadi, B., Gárdos, G.:
Effects of drugs on the calcium-dependent rapid potassium transport in calcium-loaded intact red cells,
Acta Biochim. Biophys. Acad. Sci. Hung. 13, 133-141 (1978)

16. Sarkadi, B., Schubert, A., Gárdos, G.:
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19. Sarkadi, B., Enyedi, A., Gárdos, G.:
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Molecular properties of the red cell calcium pump:II. Effects of calmodulin, proteolytic digestion and drugs on the calcium-induced membrane phosphorylation by ATP in inside-out red cell membrane vesicles.
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27. Enyedi, A., Sarkadi, B., Gárdos, G.:
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29. Enyedi, A., Faragó, A., Sarkadi, B., Szász, I., Gárdos, G.:
Cyclic AMP-dependent protein kinase stimulates the formation of polyphosphoinositides in the plasma membranes of different blood cells.
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J. Cell. Physiol. 116, 352-362, (1983)

31. Sarkadi, B., Mack, E., Rothstein, A.:
Ionic events during the volume response of human peripheral blood lymphocytes to hypotonic media: I. Distinctions between volume-activated Cl and K conductance pathways.
J. Gen. Physiol. 83, 497-512, (1984)

32. Sarkadi, B., Mack, E., Rothstein, A.:
Ionic events during the volume response of human peripheral blood lymphocytes to hypotonic media: II. Volume-and time-dependent activation and inactivation of ion transport pathways.
J. Gen. Physiol. 83, 513-527, (1984)

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34. Enyedi, A., Faragó, A., Sarkadi, B., Gárdos, G.:
Cyclic AMP-dependent protein kinase and Ca-calmodulin stimulate the formation of polyphosphoinositides in a sarcoplasmic reticulum preparation of rabbit heart.
FEBS Letters, 176, 235-238, (1984)

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Cyclic AMP-dependent protein kinase stimulates the phosphorylation of phosphatidylinositol to phosphatidylinositol-4-monophosphate in a plasma membrane preparation from pig granulocytes.
Biochem. Biophys. Res. Commun., 124, 871-876, (1984)

36. Sarkadi, B., Cheung, R., Mack, E., Grinstein, S., Gelfand, E.W., Rothstein, A.:
Cation and anion transport pathways in the volume regulatory response of human lymphocytes to hypoosmotic media.
Am. J. Physiol. 248, C480-C487, (1985)

37. Sarkadi, B., Grinstein, S., Rothstein, A., Gárdos, G.:
Analysis of Ca-induced K transport by human erythrocytes in propionate media.
Acta Biochim. Biophys. Acad. Sci. Hung., 20, 193-202, (1985)

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38. Sarkadi, B., Enyedi, A., Földes-Papp, Z., Gárdos, G.:
Molecular characterization of the in situ red cell membrane calcium pump by limited proteolysis.
J. Biol. Chem. 261, 9552-9557, (1986)

39. Enyedi, A., Sarkadi, B., Földes-Papp, Z., Monostory, S., Gárdos, G.:
Demonstration of two distinct calcium pumps in human platelet membrane vesicles.
J. Biol. Chem. 261, 9558-9563, (1986)

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Biochim. Biophys. Acta, 899, 129-133 (1987)

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J. Biol. Chem. 262, 6425-6430, (1987)

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Haematologia, 21, 33-40 (1988)

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Activation of sodium-proton exchange is not a prerequisite for Ca mobilization and aggregation in human platelets.
FEBS Letters, 225, 72-76 (1987)

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Biochim. Biophys. Acta, 939, 40-46 (1988)

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Immunol. Letters 15, 41-44, (1987)

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Effects of phosphoinositides on calcium movements in human platelet membrane vesicles.
Biochim. Biophys. Acta, 944, 202-212 (1988)

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Functional domains of the in situ red cell membrane calcium pump revealed by proteolysis and monoclonal antibodies. Possible sites of regulation by calpain and acidic lipids.
J. Biol. Chem., 264, 4577-4582 (1989)

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Immunol. Letters, 20, 47-52 (1989)

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Biochim. Biophys. Acta 984, 88-96 (1989)

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Volume regulatory mechanisms of human granulocytes in hypoosmotic media.
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51. Enouf, J., Bredoux, R., Bourdeau, N., Sarkadi, B., Levy-Toledano, S.:
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